REMARKS

Claims 10, 10, 12, 13, 18-20 and 22-24 are pending. Claims 14, 16-17, 21 and 26-30 are presently canceled without prejudice to the Applicants' right to pursue any canceled subject matter in other patent applications.

Claims 10, 12, 18 and 22 have been amended herein. The amended claims find support in the originally filed claims and specification. Accordingly, no new matter is added by the amended claims.

Claims 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement for lack of a declaration or affidavit of deposits made under the Budapest Treaty. Claims 10, 12, 14, 16, 18, 21-23, 26 and 29-30 and their dependent claims 13, 17, 19-20, 24 and 27-28 are rejected under 35 U.S.C. § 112 second paragraph for alleged indefiniteness for reciting the term "gene". Claims 10, 12, 14, 16, 18, 21-23, 26 and 29-30 and their dependent claims 13, 17, 19-20, 24 and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting the phrase "human COX-2 sequence". Claims 14, 16-17, 26-30 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting the phrase "about 1.9 kb of a human cyclooxygenase promoter". Claims 10, 12-14, 16-19, 21-22, 26-27 and 29-30 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Kutchera *et al.* (Proc. Natl. Acad. Sci. USA, 1996, Vol. 93, pp 4816-4820, henceforth referred to as "Kutchera").

Finally, claims 20, 23-24 and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kutchera in view of ATCC TIB-152 and the GibcoBRL® Catalog.

For reasons set forth below, it is respectfully requested that the rejections be withdrawn and that the pending claims be deemed allowable.

The Claims Are Enabled

Claims 23 and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." According to the Official Action, the enablement requirements under 35 U.S.C. § 112, first paragraph, may be satisfied by providing an affidavit or declaration relating to release of biological deposits made under the Budapest Treaty. The rejection should be withdrawn for the following reason.

The Applicants provide herein a Declaration by a designated representative of the depositor of the biological material. The Declaration states that the specific strains have been deposited under the Budapest Treaty under accession numbers ECACC 9903245 and CECT 5145, and that all restrictions imposed by the depositor on the availability of the deposited material will be irrevocably removed upon the granting of a patent of the microorganism(s). The person signing on behalf of Assignee, LABORATORIOS DEL DR. ESTEVE, S.A. is traveling and therefore temporarily unavailable so that the Declaration is unsigned. A signed Declaration will be provided when received by the

Attorneys for the Applicants. Accordingly, Applicants respectfully request that the rejections of Claims 23 and 24 as not sufficiently described and/or enabled under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Claims Are Definite

Claims 10, 12, 14, 16, 18, 21-23 and 29-30 and claims dependent therefrom i.e. claims 13, 17, 19-20, 24 and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner considers recitation of the term "gene" as being unclear and allegedly lacking definition in the specification.

In response, claims 10, 12 and 18 have been amended to recite the term "polynucleotide" to replace the allegedly indefinite term "gene" as suggested by the Examiner at page 3 of the Office Action. Claims 14, 16, 21 and 29-30 are canceled. Accordingly, Applicants request that the rejection be withdrawn.

Claims 10, 12, 14, 16, 18, 21-23 and 29-30 and claims dependent therefrom i.e. claims 13, 17, 19-20, 24 and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because the independent claims recite the phrase "human COX-2 sequence." The Examiner states that "[i]t is not clear ...what is encompassed by the above phrase, whether it is limited to the coding sequence, non-coding sequence, transcription controlling sequence, 5′ UTR or 3′ UTR sequences, etc."

Independent claims 10 and 18 are currently amended to read: "An isolated nucleic acid molecule having a human cyclooxygenase 2 promoter sequence operatively linked to a reporter polynucleotide, wherein the promoter sequence consists essentially of SEQ ID NO:5" thereby obviating the basis for the rejection, which should be withdrawn.

Claims 14, 16-17, 26-30 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting the phrase "about 1.9 kb of a human COX-2 promoter," at page 4 of the Office Action.

Applicants request the withdrawal of this rejection under U.S.C. § 112, second paragraph, as claims 14, 16-17 and 26-30 are presently canceled.

The Claims Are Not Anticipated

Claims 10, 12-14, 16-19, 21-22, 26-27 and 29-30 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kutchera.

The Official Action states at page 5 that Kutchera teaches: (i) a polynucleotide comprising or consisting essentially of SEQ ID NO:5 of the instant application; (ii) the polynucleotide is linked to a Renilla luciferase gene; and (iii) a cell comprising said polynucleotide. The Examiner characterizes the present claims as covering polynucleotides "comprising or consisting essentially of SEQ ID NO:5" linked to a reporter polynucleotide.

Applicants respectfully assert that the Examiner has mischaracterized the

claims as covering polynucleotides "comprising" SEQ ID NO:5, as the claims expressly recite "consisting essentially of SEQ ID NO:5," where SEQ ID NO:5 represents human cyclooxygenase 2 promoter coordinates: -1796 to +104. Kutchera teaches at page 4817, left-hand column, a sequence having coordinates -1840 to +123 of the human cyclooxygenase 2 promoter. As such, the sequence disclosed by Kutchera is neither identical to the presently claimed sequence nor to the claimed sequence with "a few additional nucleic acids," to quote the Examiner. Accordingly, Applicants assert that Kutchera does not anticipate the presently claimed invention and the rejection should be removed.

The Claims Are Not Obvious

Claims 20, 23-24 and 28 are rejected under 35 U.S.C. § 103(a) as being obvious over Kutchera as applied to claims 10, 12-14, 16-19, 21-22, 26-27 and 29-30, and further in view of ATCC TIB-152 (Jurkat cell line; a human acute T-cell leukemia cell line), and further in view of GibcoBRL® Catalog entry 16-1 (for *E. coli strain DH5*).

The Examiner has stated that "claims 20 and 23-24 are drawn to human Jurkat cells and bacterial *E. coli DH5* cells comprising a polynucleotide comprising, consisting essentially or consisting of SEQ ID NO:5 linked to a Renilla luciferase gene." The Examiner contends that: (i) Kutchera, as applied to claims 10, 12-14, 16-19, 21-22, 26-27 and 29-30, teaches a polynucleotide consisting essentially of SEQ ID NO:5 linked to the luciferase gene and utilized to examine the transcription levels of the COX-2 gene

promoter; (ii) a skilled practitioner would have recognized use of the cyclooxygenase promoter, either of Kutchera or a shorter fragment retaining full functionality following transfection into cells, for expression of said promoter in Jurkat or *E.coli DH5* cells; and (iii) utilization and availability of these cells is well known in the art and the cells are readily available through the American Type Culture Collection (ATCC) or GibcoBRL®.

Thus, according to the Examiner, combining the teachings of the above three references, it would have been obvious to one of ordinary skill in the art to (i) make a Jurkat or *E. coli DH5* cell comprising the Kutchera or shorter active promoter fragment and make a biological deposit of such cells; (ii) be motivated to use Jurkat or *E. coli DH5* cell since they are easy to grow; (iii) shorten the COX-2 promoter since shorter gene constructs are more advantageous. The Examiner states further that one of ordinary skill in the art would have had a reasonable expectation of success in making the cells since the cited reference teaches successful expression of genes in Jurkat and *E. coli DH5* cells. In addition, the Examiner alleges that a skilled practitioner would have had a reasonable expectation of success in making a shorter fragment taught by Kutchera since this reference teaches intron-exon boundaries of COX-2 and also teaches how to make fragments of a gene. Applicants respectfully disagree.

As set forth in *Graham v. Deere*, a finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the level of skill in the art, the differences between the claimed subject matter and the prior art, and whether

the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made (*Graham v. John Deere, Inc.*, 383 U.S. 1 (1966)). The art must provide both the suggestion and a reasonable expectation of success. *In re Vicki*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The prior art reference(s) must teach or suggest all the claim limitations. Both the suggestion and a reasonable expectation of success must be present in the references.

As a preliminary matter, Applicants again note that the Examiner has misconstrued the claims to apply "comprising" language to SEQ ID NO:5, where "consisting essentially of" language is used. Claim 20 relates to a Jurkat cell comprising an isolated cyclooxygenase 2 reporter polynucleotide consisting essentially of SEQ ID NO:5. Claim 23 specifies a Jurkat cell line containing an isolated cyclooxygenase 2 reporter, and claim 24 an *E. coli DH5* cell line containing an isolated cyclooxygenase 2 reporter. Cited reference Kutchera does not disclose expression of the COX-2 promoter in Jurkat or *E. coli DH5* cells. While Kutchera discloses use of a human cyclooxygenase 2 promoter fragment of approximately 2.0 kb, no rationale is presented for the choice of this particular sequence nor is any disclosure made relating to deletion analysis or what sub-regions of the disclosed 2.0 kb fragment may work as well as the parent molecule. Rather, Kutchera relates to determining whether the normally inducible human cyclooxygenase-2 gene is constitutively and abnormally activated as a result of colon cancer. Kutchera utilizes a relatively uncharacterized human cyclooxygenase-2 promoter by the standards of one skilled in the art of promoter analysis. In fact, it is well known to persons skilled in

the art of promoter analysis that change of a single nucleotide base may cause a mutation in an activator protein binding site and severely affect promoter activity. One of ordinary skill in the art would appreciate that unexpected properties may arise or an unpredictable effect may result when a promoter sequence is altered even by a few nucleotides. Iñiguez *et al.* (J Biol Chem, 2000, 275:23627-23653; Exhibit I; Ref 1 in accompanying Form 1449), FIG. 1, at page 23629, show that the promoter activity of a deletion mutation of the human cyclooxygenase 2 promoter with coordinates -170 to +140 compared to activity of the "full length" molecule from -1796 to +104 (SEQ ID NO:5) results in a promoter molecule of unpredicted higher activity. Similarly Su *et al.* (Nucleic Acids Res, 2001, 8:1661-1671, Exhibit II; Ref. 2 in accompanying Form 1449), FIG. 6, at page 1666, show that in a series of deletion mutations of a promoter, there is an unpredictable increase or decrease of activity between one deletion to the next. Thus, unless actually tested or specifically taught, it is unpredictable and no reasonable expectation of success is appropriate when using a promoter DNA sequence that differs from a previously disclosed DNA sequence.

Furthermore, there is no suggestion to combine the cited references to generate the presently claimed cell lines including biological deposits ECACC 9903245 and CECT 5145. The fact that the presently claimed promoter, truncated relative to the promoter of Kutchera, would not reasonably be expected to be active overshadows the Examiner's contention that the references would be combined because Jurkat and *E. coli DH5* cells "are easy to grow." For all these reasons, the rejection should be withdrawn.

Conclusion

Applicants respectfully request reconsideration of the application, and entry of the foregoing remarks into the file history of the above-identified application. Applicants believe that in light of the foregoing amendments and remarks, the claims are in condition for allowance, and accordingly, respectfully request withdrawal of the outstanding objections and rejections. An allowance is earnestly sought.

No additional fee is believed to be due in connection with this Response. However, should an additional fee be required, the Commissioner is hereby authorized to charge any such fee to Deposit Account No. 02-4377. Any required extension of time is hereby requested.

Respectfully submitted,

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Enclosures